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Original Scientific Paper

Diacetamides. III.* The Reaction of β- and γ-Amino Acids under the Conditions of the Dakin-West Reaction

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The reaction of β-amino acids (I) under the conditions of the Dakin-West reaction was studied. *N*-Acetyl-β-amino acids (II) and *N,N*-diacetyl-β-amino acids (III) were found to be the reaction products; III were identified as the corresponding methyl esters IV. Under the same conditions γ-aminobutyric acid (V) gave *N*-acetyl--γ-butyrolactam. Reasons for the failure of I and V to undergo the decarboxylative acetylation are discussed briefly.

The base-catalyzed conversion of α-amino acids into α-amino-ketones, commonly refered to as the Dakin-West[1] reaction, has been the subject of numerous investigations. The generally accepted mechanism[1–4] postulates *N*-acylation as the first step of the reaction; the subsequent ones comprise the cyclization to the oxazolone, the acylation of the carbanion at position 4- of the ring, and the cleavage of the latter to a β-keto acid which then decarboxylates to the ketone. However, as under identical experimental conditions some *N*-monosubstituted α-amino acids also undergo the Dakin-West reaction, a mechanism without the intermediate oxazolone, proceeding through the carbanion formed directly by decarboxylation of the *N*-acyl-α-amino acid, has also been discussed[5,6]. Anyhow, the hitherto obtained results strongly indicate that two steps, *i. e.* *N*-acylation and carbanion formation are vital for the Dakin-West reaction. The behaviour of β- and γ-amino acids under the conditions of the Dakin-West reaction has not been studied as yet. However, Baker and Ollis[7] reported that *N*-benzoyl-β-aminoisovaleric acid cyclized in acetic anhydride, without addition of a base, into the corresponding dihydro--1,3-oxazine-6-one which, unlike the related oxazolone, does not possess a reactive methylene group. On the other hand Cruickshank and Sheehan[8] investigated the reaction of *N,N*-disubstituted-γ-amino acids with carboxylic acid anhydrides. They found that depending on the nature of the substituent, two pathways, *i. e.* either decarboxylative acylation, or γ-lactam ring formation, were followed.

In connection with our work on *N,N*-diacetyl-β-aminoesters[9,10] it seemed to us of interest to examine to what extent a β-amino acid can follow the Dakin-West reaction. In addition, we included in this study also an unsubstituted γ-amino acid.

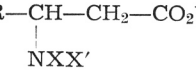
β-Alanine, β-aminobutyric acid and β-phenyl-β-aminopropionic acid (I a—c) were kept with acetic acid anhydride and pyridine at 100° and at reflux

* Part II, A. Kornhauser, D. Keglević, and O. Hadžija, *Croat. Chem. Acta* **34** (1962) 167.

temperature respectively, for 2—6 hours. Quantitative estimation of CO_2 in effluent gases gave values which never exceeded the blanks. In parallel experiments, under identical conditions, α-aminobutyric acid evolved 54% of CO_2 at 100°, and 78% of CO_2 at reflux temperature over a period of 6 hours.

Thin-layer chromatography (TLC) of the reaction product revealed several spots none of which was the starting β-amino acid. On alumina and silicagel columns the reaction product decomposed; however on a charcoal-celite column it could be resolved into two fractions. The major one was identified as the corresponding *N*-acetyl-β-amino acid (II a—c); the minor contained an acidic unstable compound. The latter was converted by diazomethane into a neutral distillable product the IR spectrum of which showed the absence of NH bands and the presence of a doublet at 5.75, 5.85 μ, characteristic for diacetamide[9]; it was identified as the corresponding *N,N*-diacetyl-β-amino methyl ester (IV a—c).

Hence, β-amino acids under the conditions of the Dakin-West reaction undergo only *N*-acetylation yielding *N*-acetyl-β-amino acids (II) and *N,N*-diacetyl-β-amino acids (III) as the reaction products.



I X = X′ = Y = H III X = X′ = Ac, Y = H
II X = Ac, X′ = Y = H IV X = X′ = Ac, Y = Me

R (a) = H; (b) = Me; (c) = Ph

The yields on II ranged from 50—60% and those on III, calculated from the methyl esters IV, from 18—25%. Prolonged heating as well as the use of II as the starting compound did not change substantially these values.

The fact that β-amino acids follow only the first step of the Dakin-West reaction can be explained by the spatial distance between the amino and carboxylic group; apparently the activiting effect of the latter on the enolizable β-acetamino group is largely diminished. In addition, the nature of the *N*-acyl substituent seems to exert also a marked influence upon the relative easiness of cyclization: when Ia was treated as claimed[7] for *N*-benzoyl-β-aminoisovaleric acid, again the dihydro-oxazinone ring was not formed.

The reaction of γ-aminobutyric acid (V) in acetic anhydride — pyridine at 100° proceeded without the evolution of carbon dioxide too. From the reaction mixture, after carbon-celite chromatography, an oil identified as *N*-acetyl-γ-butyrolactam (VI) was isolated in 75% yield. Neither γ-butyrolactam nor any ketonic product could be detected. In order to get some information whether the acetylation preceeded the cyclization or *vice versa*, the reaction was carried out for 20 minutes at 60° and 40°, respectively. In both cases besides VI, *N*-acetyl-γ-aminobutyric acid was identified. Thus, under the conditions of the Dakin-West reaction V is first acetylated and then cyclized into the lactam ring; as VI lacks an additional activation of the α-methylene group the *C*-acetylation cannot take place.

EXPERIMENTAL

Materials and Methods

1. Carbon-celite powder. Charcoal (BDH, activated) was treated according to Schramm and Primosigh[11]. After careful drying over P_2O_5, an intimate (1 : 1.5) mixture of carbon and celite (BDH) was prepared.

2. Determination of CO_2. The reflux condenser of the apparatus was connected with a trap cooled in a dry ice-acetone bath, followed by one anhydrone and two alternatively connected ascarite tubes, which were changed at 2 hours intervals. Dry, CO_2 free, nitrogen was passed through the system during the reaction.

3. TLC (ascending) was carried out using silicagel G (Merck) in the following solvent systems: (*A*) butanol—acetic acid—water, (65 : 15 : 25); (*B*) methanol—water, (95 : 5); (*C*) chloroform; (D) ether. The plates were developed by exposure to iodine vapour, or by spraying with ninhydrin, or with bromocresole-green (0.1% in ethanol + 1 drop of morpholine).

4. Unidimensional paper electrophoresis on Whatman No 1 paper was performed at room temperature, with a voltage gradient of 12 V per cm. in pyridine acetic acid buffer (*p*H 6.5).

Reaction of β-Amino Acids with Acetic Anhydride in Pyridine

The β-amino acid (I a—c, 30 mmoles) was suspended in 24 ml. of acetic anhydride and 12 ml. of pyridine, and the mixture was kept at 100° (oil bath) for approximately 3 hours. Acetic anhydride-pyridine was distilled off on a rotary evaporator at 40°/12 mm. and then at 40°/0.01 mm. The dark oily residue was dissolved in hot acetone and treated with charcoal. After the removal of the solvent a viscous amber oil remained which was dissolved in a minimum amount of benzene and put on a charcoal-celite column (50 × 2 cm.) prepared with benzene. The same solvent eluted a colourless oil (benzene fraction) which persisted all attempts of purification. Further elution of the column with acetone displaced in a sharp peak the corresponding *N*-acetyl-β-amino acid (II a—c).

Treatment of the Benzene Fraction with Diazomethane. Methyl Esters of N,N-*Diacetyl-β-amino acids* (IV a—c)

The benzene fraction (1.5—2.0 g.) was dissolved in 10 ml. ether and treated with an ethereal solution of diazomethane (100 mmoles) in the standard way. The solvent was removed, the remaining oil distilled *in vacuo* and the distillate chromatographed on a silicagel (Merck) column (37 × 1.5 cm.) prepared with ether. Elution with the same solvent gave the corresponding *N,N*-diacetyl-β-amino ester IV.

Reaction with β-Alanine (I a). *N*-Acetyl-β-alanine (II a) was isolated in 52% yield, m. p. 76—78° (from ethyl acetate): undepressed melting point and superimposable IR spectrum with an authentic sample.

Methyl *N,N*-diacetyl-β-aminopropionate (IV a) was obtained *via* III a in 20% yield (calc'd. on I a). For analysis it was distilled at 75—78°/0.015 mm. IR spectrum: 5.75, 5.85 μ (CO).

Anal. $C_8H_{13}NO_4$ (187.20) calc'd: C 51.33; H 7.00; N 7.48%
found: C 51.04; H 7.01; N 7.63%

Reaction with β-Aminobutyric Acid (I b). *N*-Acetyl-β-aminobutyric acid (II b) was isolated as a heavy syrup in 55% yield; superimposable IR spectrum and no depression of its dicyclohexylamine salt with authentic samples.

Methyl *N,N*-diacetyl-β-aminobutyrate (IV b) was obtained in 16% yield. For analysis it was distilled at 73—75°/0.01 mm. IR spectrum: 5.75, 5.90 μ (CO).

Anal. $C_9H_{15}NO_4$ (201.23) calc'd.: C 53.72; H 7.51; N 6.96; acetyl 42.80%
found: C 53.94; H 7.40; N 7.25; acetyl 42.70%

Reaction with β-Amino-β-phenylpropionic Acid (I c). N-Acetyl-β-phenyl-β-aminopropionic acid (II c) was isolated in 60% yield; m. p. 158—160° (from ethanol), undepressed m. p. and superimposable IR spectrum with an authentic sample[12].

Methyl *N,N*-diacetyl-β-amino-β-phenylpropionate (IV c) was obtained in 15% yield; for analysis it was distilled at 115—120°/0.01 mm. IR spectrum: 5.75, 5.90 μ (CO).

Anal. $C_{14}H_{17}NO_4$ (263.29) calc'd.: C 63.86; H 6.51; N 5.32%
found: C 63.83; H 6.41; N 5.24%

N-*Acetyl-β-Amino Acids* (II a—c)

To a cooled solution of the appropriate β-amino acid (10 mmoles) in 2 ml. of acetic anhydride and 8 ml. 2 *N* NaOH, 1.6 ml. of acetic anhydride and 8 ml. 2 *N* NaOH

were alternatively added under shaking and cooling at 0°. After standing overnight at room temp., 50 ml. of water was added, the solution was passed through Dowex 50-X8 H^+ and the resin was washed with water to neutral reaction. After the removal of water, the residue was treated as described below.

N-*Acetyl-β-alanine* (II a), yield 76%, white crystals, m. p. 77—78° from ethyl acetate. King and King[13] give m. p. 78.3—80.3° without experimental data.

N-*Acetyl-β-aminobutyric acid* (II b), yield 90% of a syrup which could not be brought to crystallisation. IR spectrum: 3.0 (NH), 5.80 (CO), 6.20 (CO), 6.45 μ (amide II). A sample was converted into dicyclohexylamine salt by the standard procedure: m. p. 146—148° from ethanol-ether.

Anal. $C_{18}H_{34}N_2O_3$ (326.48) calc'd.: C 66.22; H 10.50; N 8.81%
found: C 66.04; H 10.23; N 8.81%

Reaction of γ-Aminobutyric Acid (V) *with Acetic Anhydride and Pyridine*

γ-Aminobutyric acid (3.0 g., 30 mmoles) was suspended in a mixture of 24 ml. acetic anhydride and 12 ml. pyridine and treated in the same way as described for β-amino acids. The elution of the charcoal-celite column with benzene gave an oil, b. p. 70—72°/0.01 mm., (2.9 g., 75%) which was identified by elemental analysis as *N*-acetyl-γ-butyrolactam (VI). IR spectrum: 5.75, 5.95 μ (CO), superimposable with an authentic sample[14].

For the detection of *N*-acetyl-γ-aminobutyric acid, the reaction mixture was subjected to paper electrophoresis. The spots were visualized with Cl_2-starch-KI reagent[15].

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IZVOD

Diacetamidi III. Reakcije β- i γ-amino kiselina pod uslovima Dakin-West reakcije

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Nađeno je da β-amino kiseline (I) pod uvjetima Dakin-West reakcije ne podliježu dekarboksilativnoj acilaciji, već da su produkti reakcije odgovarajuće *N*-acetil- i *N,N*-diacetilamino kiseline (II i III); III su identificirani kao metil esteri (IV). Pod istim uvjetima γ-amino maslačna kiselina (V) daje *N*-acetil-γ-butirolaktam; utvrđeno je da prvo dolazi do acetilacije a zatim do ciklizacije. Diskutirani su uzroci zbog kojih I i V ne podliježu Dakin-West reakciji.

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